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Biological Effects of *Myristica fragrans*

Preetee Jaiswal, Pradeep Kumar, Vinay K Singh, Dinesh K Singh*

Department of Zoology, DDU Gorakhpur University, INDIA

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Abstract

Jaiswal P, Kumar P, Singh VK, Singh DK. Biological Effects of Myristica fragrans. Annu Rev Biomed Sci 2009;11:21-29. *Myristica fragrans* is an evergreen tree that produces two spices, nutmeg and mace. Its medicinal uses in the aurvedic system of treatment are based on traditional experience inherited from one generation to other. Scientists from various disciplines are now directing their research towards investigating the effects of *M. fragrans* on human health. The chemical constituents of *M. fragrans* have been investigated for hypolipidaemic and hypocholesterolemic effects, antimicrobial, antidepressant, aphrodisiac, memory enhancing, antioxidant and hepatoprotective properties. Recent studies have revealed strong insecticidal and molluscicidal activities of *M. fragrans*. Despite some laboratory studies on the insecticidal / molluscicidal activity of *M. fragrans*, more field studies are recommended for effective control of pests. It is clearly evident from the literature review that *M. fragrans* deserves more attention by scientific community and public health specialists to explore its full range of benefits in the welfare of the society.

Keywords: *Myristica fragrans,* nutmeg, mace, antimicrobial, antioxidant, pesticidal

Table of Contents

***Correspondence**
Dinesh K Singh. Reader, Department of Zoology, DDU Gorakhpur University, Gorakhpur-273 009, UP, India.
E-mail: dksingh_gpu@yahoo.co.in

1. Introduction

Myristica fragrans Houtt., commonly known as Jaiphal and Javitri in India, belongs to the family Myristicaceae. It produces two spices, nutmeg and mace. Nutmeg is the seed kernel inside the fruit and mace is the fleshy red, net like skin covering (aril) on the kernel. It is a spreading aromatic evergreen tree usually growing to 5 to 13 metres high, occasionally 20 metres. The pointed dark green leaves are arranged alternately along the branches and are borne on leaf stems about 1 cm long. Upper leaf surfaces are shiny. Flowers are usually single sexed; occasionally male and female flowers are found on the same tree. Female flowers arise in groups of 1 to 3; males in groups of 1 to 10. Flowers are pale yellow, waxy, fleshy and bell-shaped. The fruits are fleshy, drooping, yellow, smooth, 6 to 9 cm long with a longitudinal ridge. When ripe, the succulent yellow fruit coat splits into 2 valves revealing a purplish-brown, shiny seed (nutmeg) surrounded by a red aril (mace). Seeds (nutmegs) are broadly ovoid (2 to 3 cm long), firm, fleshy, whitish and transversed by red-brown veins. When fresh, the aril (mace) is bright scarlet becoming more horny, brittle and a yellowish-brown colour when dried (Purseglove, 1968). The trees do not give flowers until around 9 years old, but once start flowering they continue to do so for further 75 years. The trees bear 2 to 3 crops a year. The seeds (nutmegs) need 3 to 6 weeks to dry before they are ready for use.

1.1. Distribution

Indigenous to the Moluccas and Banda Islands in the South Pacific, it is seldom found truly wild. It is now cultivated in tropical regions, especially in Indonesia, Grenada in the West Indies and Sri Lanka (Purseglove, 1968; Bown, 1995).

1.2. Pharmacologically active parts of the plant

The most important part of the plant in terms of its pharmacological activity and also in commerce, is of course the dried kernel (seed), the nutmeg. Intoxication from the use of the aril of the fruit (seed case), generally known as mace, has also been reported, but only rarely. The oil of nutmeg has also been used for medicinal purposes and it is this fraction of the nutmeg which contains the pharmacologically active components. It is used as a spice in various dishes, as components of tea and soft drinks or mixed in milk and alcohol. In traditional medicine nutmeg is sometimes used as a stomachic, stimulant, carminative as well as for intestinal catarrh and colic, to stimulate appetite, to control flatulence and it has a reputation as an emmenagogue and abortifacient (Nadkarni, 1988). Mace is widely used as a flavouring agent, a hair dye and a folk medicine. It also possesses antipapillomagenic, anticarcinogenic (Hussain & Rao, 1991) and anti-inflammatory activities (Ozaki *et al*., 1989).

2. Chemical Composition

The main constituents of *M. fragrans* have been found to be alkyl benzene derivatives (myristicin, elemicin, safrole etc.), terpenes, alpha-pinene, beta-pinene, myristic acid and trimyristin (Qiu *et al*., 2004; Wang *et al*., 2004; Forrester, 2005; Yang *et al*., 2008). Nutmeg contains about 10% essential oil, which is mostly composed of terpene hydrocarbons (sabinene and pinenes; furthermore camphene, *p*-cymene, phellandrene, terpinene, limonene, myrcene, together 60 to 80%), terpene derivatives (linalool,

geraniol, terpineol, together 5 to 15%) and phenylpropanoids (myristicin, elemicin, safrole, eugenol and eugenol derivatives, together 15 to 20%). Of the latter group, myristicin (methoxy-safrole, typically 4%) is responsible for the hallucinogenic effect of nutmeg. Oil of mace (up to 12% in the spice) contains the same aroma components but the total fraction of terpenoids is increased to almost 90%. Both nutmeg and mace contain about 2% of lignans (diarylpropanoids), which are non volatile dimers of phenylpropanoid constituents of the essential oil, *e.g.* dehydrodiisoeugenol (Anonymous, 1995). The main glycoside is trimyristin having anxiogenic activity (Sonavane *et al*., 2002).

3. Biological Effects

In India, spices have been traditionally used since ancient times, for the preservation of food products as they have been reported to have antiseptic and disinfectant properties (De *et al*., 1999). In the traditional Indian medical science of Ayurveda, nutmeg is said to possess antidiarrhoeal activity. Both nutmeg and mace are used as condiment and in medicine (Nadkarni, 1988). Nutmeg is stimulant, carminative, astringent and aphrodisiac; it is used in tonics and electuaries and forms a constituent of preparations prescribed for dysentery, stomach ache, flatulence, nausea, vomiting, malaria, rheumatism, sciatica and early stages of leprosy. Excessive doses have a narcotic effect; symptoms of delirium and epileptic convulsions appear after 1-6 hours (Anonymous, 1995; Hang & Yang, 2007). It is widely believed that myristicin is the major component responsible for intoxications (Hallstrom & Thuvander, 1997). Myristicin is toxic when ingested in large amounts, and it is liable to cause fatty degeneration of the liver (Anonymous, 1995; Beyer *et al*., 2006). Lee *et al*. (2005) have reported that myristicin (1-allyl-3,4-methylenedioxy-5-methoxybenzene), a naturally occurring allylbenzene found in nutmeg induces cytotoxicity in human neuroblastoma SK-N-SH cells by an apoptotic mechanism. Trimyristin shows anxiogenic activity (Sonavane *et al*., 2002). Trimyristin and myristicin isolated from *M. fragrans* seeds exhibit good antibacterial activity against Gram-positive and Gram-negative bacteria (Narasimhan & Dhake, 2006).

Grover *et al*. (2002) have studied the pharmacological effects of nutmeg and found that the extracts of nutmeg show a good antidiarrhoeal effect, with a significant sedative property. The extracts also possess a weak analgesic effect, with no harmful effects on blood pressure and ECG. Jan *et al*. (2005) have evaluated the effects of extract of *M. fragrans* and verapamil on the volume and acidity of carbachol induced gastric secretion in fasting rabbits. It has been found that the extract from *M. fragrans* which contains documented natural calcium channel blocker reduces the volume, free and total acidity of gastric secretion. Verapamil also has the same effects. Thus, the effect of *M. fragrans* is similar to verapamil and therefore it can be effectively used in the treatment of peptic ulcer and all other conditions that require calcium channel blockers for the treatment of these disorders.

3.1. Antimicrobial activity

M. fragrans (nutmeg and mace) is known to exhibit strong antimicrobial activity against animal and plant pathogens, food poisoning and spoilage bacteria including *Bacillus subtilis*, *Escherichia coli*, *Saccharomyces cerevisiae*, multi-drug resistant *Salmonella typhi* and *Helicobacter pylori* (Orabi *et al*., 1991; De *et al*., 1999; Dorman & Deans, 2000; Rani & Khullar, 2004; Mahady *et al*., 2005; O'Mahony *et al*., 2005). Alcoholic extracts of nutmeg show anti-bacterial activity against *Micrococcus pyogens* var. *aureus* (Anonymous, 1995). Essential oil of nutmeg caused a significant inhibition of growth and survival of *Yersinia enterocolitica* and *Listeria monocytogenes* in broth culture and in Iranian barbecued chicken (Firouzi *et al*., 2007).

Takikawa *et al*. (2002) have reported the antimicrobial activity of nutmeg (seeds of *M. fragrans*) extract against *Escherichia coli* O157. When the *E. coli* strains are incubated with spice extract at concentrations of 0.01% and 0.1%, a noteworthy difference has been observed between the O157 *E. coli* and non-pathogenic *E. coli* strains to their tolerance to nutmeg. The populations of the non-pathogenic strains can not be reduced, but those of the O157 strains are remarkably reduced. Antibacterial activity of nutmeg extract was also found against the enteropathogenic *E. coli* O111, but not against enterotoxigenic (O6 and O148) and enteroinvasive (O29 and O124) *E. coli*. When they have examined

the antibacterial effect of volatile oils of nutmeg on the O157 and non-pathogenic *E. coli* strains, all O157 strains tested were found to be more sensitive to beta-pinene than non-pathogenic *E. coli* strains. Aqueous extract of nutmeg has bactericidal activity against *Helicobacter pylori* (O'Mahony *et al*., 2005). *H. pylori* infections are associated with the development of gastritis, dyspepsia, peptic ulcer disease, gastric carcinoma and primary gastric B-cell lymphoma. Mahady *et al*. (2005) have studied the *in vitro* susceptibility of 15 *H. pylori* strains to botanical extracts. It has been found that methanol extract of *M. fragrans* (seed), having a MIC of 12.5 µg/ml against *H. pylori* strains, is highly effective in the treatment of gastrointestinal disorders. Rani and Khullar (2004) have reported strong antibacterial activity of methanol extract of *M. fragrans* against multi-drug resistant *Salmonella typhi*. Nutmeg has potent antimicrobial activity against *Bacillus subtilis* (ATCC 6633), *Escherichia coli* (ATCC 10536) and *Saccharomyces cerevisiae* (ATCC 9763) (De *et al*., 1999). The volatile oils of *M. fragrans* exhibit considerable inhibitory effects against different genera of bacteria including animal and plant pathogens, food poisoning and spoilage bacteria (Dorman & Deans, 2000). At 35°C, food-borne pathogen, *Listeria monocytogenes* is extremely sensitive to the oil of nutmeg (Smith-Palmer *et al*., 1998). The two antimicrobial resorcinols malabaricone B [1] and malabaricone C [2] isolated from mace have been reported to exhibit strong antifungal and antibacterial activities (Orabi *et al*., 1991). Malabaricone C isolated from *M. fragrans* (nutmeg) irreversibly inhibits Arg-gingipain by 50% at a concentration of 0.7 µg/ml and selectively suppressed *Porphyromomas gingivalis* growth (Shinohara *et al*., 1999). Macelignan isolated from *M. fragrans* is a potent natural anti-biofilm agent against oral primary colonizers *Streptococcus sanguis* and *Actinomyces viscosus*. These colonizers initially attached to the pellicle-coated tooth surface to form a biofilm. Treatment with 10µg/ml of macelignan caused 30% reduction in growth of these colonies within 5 minute (Yanti *et al*., 2008). Cho *et al*. (2007) have isolated three lignans erythro-austrobailignan-6, meso-dihydroguaiaretic acid and nectandrin-B from *M. fragrans* seeds. These lignans were effective against *Alternaria alternata*, *Colletotrichum coccodes*, *C. gloeosporioides*, *Magnaporthe grisea*, *Agrobacterium tumefaciens*, *Acidovorax konjaci* and *Burkholderia glumae* in *in vivo* and *in vitro* conditions.

Rotaviruses have been recognized as the major agents of diarrhoea in infants and young children in developed as well as developing countries. Goncalves *et al*. (2005) have studied *in vitro* anti-rotavirus activity of some medicinal plants used in Brazil against diarrhoea. It was found that the extracts from *M. fragrans* seeds inhibited human rotavirus (90% inhibition) at concentration of 160 µg/ml. Thus *M. fragrans* can be useful in the treatment of human diarrhea, if the etiologic agent is a rotavirus.

3.2. Hypolipidaemic and hypocholesterolemic effect

The ethanolic extract of *M. fragrans* (nutmeg) shows hypolipidaemic effect on experimentally induced hyperlipidaemia in albino rabbits. Ram *et al*. (1996) have reported that an oral administration of nutmeg extract at the dose of 500 mg/kg body weight to hyperlipidaemic albino rabbits for 60 days significantly reduced the lipoprotein lipids level. Sharma *et al*. (1995) have reported that administration of *M. fragrans* seed extract to hypercholesterolemic rabbits reduced serum cholesterol and LDL cholesterol by 69.1 and 76.3%, respectively and also lowered cholesterol/phospholipid ratio by 31.2% and elevated the decreased HDL-ratio significantly. It is also known to prevent the accumulation of cholesterol, phospholipids and triglycerides in liver, heart and aorta and dissolves atheromatous plaques of aorta by 70.9-76.5%. Removal of cholesterol and phospholipids in fecal matter is significantly increased in rabbits fed with seed extract of *M. fragrans*.

3.3. Antidepressant activity

Dhingra and Sharma (2006) determined the antidepressant activity of *n*-hexane extract of *M. fragrans* seeds in mice using the forced swim test (FST) and the tail suspension test (TST) at three dose level 5, 10, and 20 mg/kg body weight. The 10 mg/kg dose was found to be most potent, as indicated by the highest decrease in the immobility period compared with the control. Furthermore, this dose of the extract was found to have comparable potency to imipramine (15 mg/kg) and fluoxetine (20 mg/kg). Thus, the extract of *M. fragrans* is capable to elicit a significant antidepressant-like effect in mice, when assessed by both TST and FST. The antidepressant-like effect of the extract seems to be mediated by interaction with the adrenergic, dopaminergic and serotonergic systems.

3.4. Antidiabetic activity

Macelignan is a natural compound isolated from *M. fragrans*. It enhanced the insulin sensitivity and improved lipid metabolic disorders by activating peroxisome proliferator receptor (PPAR, á/ã) and attenuating endoplasmic reticulum stress, suggesting that it is an antidiabetic agent for the treatment of type 2 diabetes (Han *et al*., 2008).

3.5. Aphrodisiac activity

In Unani medicine, *M. fragrans* (nutmeg) has been mentioned to be of value in the management of male sexual disorders. In an experimental study, Tajuddin *et al*. (2005) have found that the oral administration of 50% ethanolic extract of nutmeg at 500 mg/kg body weight produces a significant and sustained increase in the sexual activity of normal male rats without any conspicuous adverse effects, which might be attributed to its nerve stimulating property.

3.6. Cytotoxicity

Lee *et al*. (2005) have reported that myristicin (1-allyl-3,4-methylenedioxy-5-methoxybenzene), a naturally occurring alkyl benzene derivative found in nutmeg induces cytotoxicity in human neuroblastoma SK-N-SH cells by an apoptotic mechanism. It was observed that a dose-dependent reduction in cell viability occurred at myristicin concentration > or =0.5 mM in SK-N-SH cells. The apoptosis triggered by myristicin was accompanied by an accumulation of cytochrome-c and by the activation of caspase-3. Chirathaworn *et al*. (2007) observed that the methanolic extract of *M. fragrans*, even 10 µg/ml, induces apoptosis of Jurkat leukemia T cell line through SIRT1 mRNA down regulation.

3.7. Memory enhancing activity

Parle *et al*. (2004) have investigated the effect of *M. fragrans* seeds on learning capabilities and memory level in mice. The learning and memory parameters were assessed using elevated plus-maze and passive-avoidance apparatus. Administration of the *n*-hexane extract of *M. fragrans* at the lowest dose of 5 mg/kg body weight for 3 successive days significantly improved the learning and memory level of young and aged mice. The extract also reversed scopolamine and diazepam-induced impairment in learning and memory of young mice. The observed memory enhancing effect of *M. fragrans* may be attributed to a variety of properties (individually or in combination) such as antioxidant, anti-inflammatory, or perhaps procholinergic activity.

3.8. Antioxidant activity

Murcia *et al*. (2004) have evaluated the antioxidant properties of some spices and compared with those of the common food antioxidants butylated hydroxyanisole (BHA) (E-320), butylated hydroxytoluene (BHT) (E-321) and propyl gallate (E-310). Nutmeg, anise and licorice showed the strongest protection in the deoxyribose assay. Nutmeg, propyl gallate, ginger and licorice improved the stability of oils (sunflower, corn, and olive) and fats (butter and margarine) against oxidation (110°C). When the Trolox equivalent antioxidant capacity (TEAC) assay was used to provide a ranking order of antioxidant activity, the antioxidant capacity of nutmeg was found to be higher than BHT. Murcia *et al*. (2004) reported that phenylpropanoid compound extracts from nutmeg possessed antioxidant activity. Recently Checker *et al*. (2008) observed that lignans present in aqueous extract of fresh nutmeg mace possess antioxidant, radioprotective and immunomodulatory effects in mammalian cells. High antioxidant activity has been reported in monoterpenoid rich extracts such as terpinene-4-ol, alpha-terpineol and 4-allyl-2,6-dimethoxyphenol in nutmeg seed (Maeda *et al*., 2008).

Yadav and Bhatnagar (2007) reported that aril part of *M. fragrans* have significant antioxidant activity due to its ability to inhibit lipid peroxidation and superoxide radical scavenging activity in rat. Pretreatment with *M. fragrans* effectively protects the mice against radiation-induced biochemical alterations as evident by decrease in lipid peroxidation level and acid phosphatase activity and simultaneous increase in hepatic glutathione and alkaline phosphatase activity (Sharma & Kumar, 2007).

3.9. Hepatoprotective activity

Morita *et al*. (2003) have reported that myristicin from *M. fragrans* (nutmeg) possessed most potent hepatoprotective activity to rats with liver damage induced by lipopolysaccharide (LPS) plus D-galactosamine (D-GalN). It was also found that myristicin markedly suppressed LPS/D-GalN-induced enhancement of serum TNF-alpha concentrations and hepatic DNA fragmentation in mice. These findings suggest that the hepatoprotective activity of myristicin may be, at least in part, due to the inhibition of TNF-alpha release from macrophages. Sohn *et al*. (2008) observed that the hepatoprotective effects of macelignan, isolated from *M. fragrans* is related to activation of the mitogen activated protein kinase (MAPK) signaling pathway, especially JNK and c-Jun.

3.10. Pesticidal activity

3.10.1. Insecticidal

Jung *et al*. (2007) have reported the insecticidal properties of *M. fragrans* seed compounds against adult females of *Blattella germanica* (Dictyoptera: Blattellidae). Myristicin present in the kernel may be employed as an additive to pyrethrum to enhance the toxicity of the latter to houseflies, although myristicin itself is inactive (Anonymous, 1995). The aqueous decoctions of *M. fragrans* have been found to be toxic to cockroaches (Anonymous, 1995). Essential oil of *M. fragrans* has insecticidal activity against larvae of *Lycoriella ingenua* (Park *et al*., 2008) and *Callosobruchus chinensis* (Chaubey, 2008).

3.10.2. Molluscicidal

Jaiswal and Singh (2009) reported that *M. fragrans* seed and aril i.e., nutmeg and mace are potential source of botanical molluscicides against *Lymnaea acuminata*. These snails are the intermediate host of liver fluke *Fasciola hepatica* and *F. gigantica*, which causes 94% fascioliasis in the buffalo's population of northern India (Singh & Agarwal, 1981; Singh & Agarwal, 1983). The active molluscicidal components of nutmeg and mace are soluble in chloroform, acetone and ethanol but the molluscicidal components in nutmeg are insoluble in carbon tetrachloride and ether. Usually toxicity of mace powder against *L. acuminata* is higher than that of nutmeg powder. Jaiswal and Singh (2009) characterized that trimyristin and myristicin are the main molluscicidal components of nutmeg and mace. The toxicity of myristicin was found to be 43.81 times higher than trimyristin after 96h.

LC_{50} (96h) of column purified fraction of nutmeg (3.98 mg/l) and mace (2.77 mg/l) against *L. acuminata* are lower than the LC_{50} (96h) values of synthetic molluscicides- carbaryl (4.40 mg/l), phorate (15.0 mg/l), formothion (8.56 mg/l) (Singh & Agarwal, 1983) and aldicarb (11.50 mg/l) (Singh & Agarwal, 1981). 96h LC_{50} of crude powder of nutmeg (36.95 mg/l) and mace (28.61 mg/l) against *L. acuminata* are lower than the crude powder of common spices, *Allium sativum* bulb (271.06 mg/l), *Zingiber officinale* rhizome (273.80 mg/l), *Trachyspermum ammi* (97.59 mg/l), *Allium cepa* bulb (253.27 mg/l), *Cinnamomum tamala* leaf (830.90 mg/l), *Ferula asafoetida* dried latex powder (82.71 mg/l) and *Syzygium aromaticum* flower bud (51.98 mg/l) (Singh & Singh, 1995; Singh *et al*., 1997; Srivastava & Singh, 2005; Kumar & Singh, 2006).

Dhingra *et al*. (2006) demonstrated that the *n*-hexane extract of the seeds of *M. fragrans* significantly inhibited AChE activity in brain of Swiss albino mice. Mukherjee *et al*. (2007) reported that in *in vitro* hydroalcoholic extracts of *M. fragrans* inhibited 50% of AChE activity at concentration of 100-150 µg/ml using AChE obtained from bovine erythrocytes. Jaiswal *et al*. (2009) demonstrated that *in vivo* treatment of snail with sublethal concentrations (40% and 80% of 24h and 96h LC_{50}) of trimyristin and myristicin caused significant ($P < 0.05$) inhibition in AChE (acetylcholinesterase), ACP (acid phosphatase) and ALP (alkaline phosphatase) activity in the nervous tissue of *Lymnaea acuminata.* Inhibition of these enzymes by trimyristin and myristicin in the nervous tissue of *L. acuminata* is the major cause of the molluscicidal activity of *Myristica fragrans*.

3.11. Clinical effects

In human, nutmeg intoxication resembles to intoxication due to excessive intake of anticholinergic agents, *e.g.* profuse sweating, flushed face, delirium, dry throat etc. There is always an

altered state of mind, *e.g.* hallucinations, confusion and an impending sense of doom. Clinical symptoms may be contradictory depending on the length of time lapsed after ingesting the toxin. Symptoms also vary according to the dose taken and the variability between different samples of nutmegs.

4. Conclusion

Information from extensive literature review indicates that *M. fragrans* has a broad spectrum of pharmacological effects. A single spice has the potential of curing a large number of diseases. Nutmeg and mace produced from *M. fragrans* are very effective against various animal and plant bacteria, fungi and harmful viruses, insects and snails. The antidepressant, aphrodisiac, antioxidant and hepatoprotective activities of *M. fragrans* are well accepted because of the wealth of scientific literature supporting these effects. Instead of several tests on rats / rabbits, *M. fragrans* is not yet widely used against man. More research should be undertaken to determine its efficacy against several diseases on man with respect to other natural products and modern drugs. Therefore, *M. fragrans* deserves more attention by scientific community and public health specialists to explore its full range of benefits in the welfare of the society.

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